AMENDMENTS TO THE SPECIFICATION

Please amend the paragraphs on page 5, lines 11-18 as follows:

~~16. Adenovirus according to claims 14 or 15, whereby~~ In a preferred embodiment of the second aspect the adenoviral promoter is the E1A promoter.

~~17. Adenovirus according to any of claims 6 to 16, characterized in that~~ In an embodiment of the second aspect the expression of the E1A protein is controlled by a promoter, whereby the promoter is selected from the group comprising tumor-specific promoters, organ-specific promoters, tissue-specific promoters, heterologous promoters and adenoviral promoters, whereby the adenoviral promoter is different from the E1A promoter.

Please insert the following paragraph on page 6, line 19, after the paragraph ending "...the E4 region and combinations thereof" as follows:

In an embodiment of the fifth aspect the adenovirus is an adenovirus in accordance with the first and/or second and/or third and/or fourth aspect of the present invention.

Please insert the following paragraph on page 7, line 15, after the paragraph ending "preferably an E4orf6 protein" as follows:

In an embodiment of the seventh aspect the adenovirus is an adenovirus according to the first and/or second and/or third and/or fourth and/or fifth and/or sixth aspect of the present invention.

Please insert the following paragraphs on page 14, line 28, after the paragraph ending "optionally a pharmaceutically acceptable carrier" as follows:

In a twenty-first aspect the problem underlying the present invention is solved by the use of a virus, preferably an adenovirus, for the manufacture of a medicament, whereby the virus is replication deficient in normal cells which do not contain YB-1 in the nucleus, in cells which do not contain YB-1 in the nucleus independent of the cell cycle, and in cells which do not contain deregulated YB-1, respectively, and the virus codes for an oncogene or oncogene product, in particular an oncogene protein which at least

transactivates one viral gene in YB-1 nucleus positive cells, preferably an adenoviral gene, whereby the gene is selected from the group comprising E1B55kDa, E4orf6, E4orf3 and E3ADP. Preferably, the virus expresses the viral proteins E1B55kD, which is also referred to herein as E1B55kDa, and E4orf6.

In a twenty-second aspect the problem underlying the invention is solved by the use of a virus, preferably an adenovirus, for replication in cells, which contain YB-1 in the nucleus, whereby the virus is replication deficient in cells which do not contain YB-1 in the nucleus, or cells which do not contain YB-1 in the nucleus independent of the cell cycle, or cells which do not contain any deregulated YB-1, and whereby the virus codes for an oncogene or an oncogene product, in particular an oncogene protein, which transactivates at least one viral gene, preferably an adenoviral gene, whereby the gene is selected from the group comprising E1B55kDa, E4orf6, E4orf3 and E3ADP.

In an embodiment of the uses in accordance with the twenty-first and twenty-second aspect of the invention the virus, in particular the adenovirus, replicates in cells which contain YB-1 in the nucleus or which do not contain YB-1 in the nucleus independent of the cell cycle, or which do not comprise any deregulated YB-1.

In a further embodiment of the uses in accordance with the twenty-first and twenty-second aspect of the invention the viral oncogene protein is E1A and/or the oncogene is the gene coding for E1A and/or the oncogene protein is E1A.

In a preferred embodiment the viral oncogene protein E1A is capable of binding a functional Rb tumor suppressor gene product.

In an alternative embodiment the viral oncogene protein E1A is incapable of binding a functional Rb tumor suppressor gene product.

In a further embodiment of the uses in accordance with the twenty-first and twenty-second aspect of the invention the viral oncogene protein E1A does not induce nuclear localisation of YB-1.

In a further embodiment of the uses in accordance with the twenty-first and twenty-second aspect of the invention the medicament is for patients the cells of which are either Rb positive or Rb negative.

In a preferred embodiment the cells are those cells involved in the formation of the condition which is to be affected by the medicament.

In a further embodiment of the uses in accordance with the twenty-first and twenty-second aspect of the invention the cells are Rb-negative and YB-1-positive in the nucleus, in particular are YB-1 positive in the nucleus independent of the cell cycle.

In a still further embodiment of the uses in accordance with the twenty-first and twenty-second aspect of the invention the medicament is for the treatment of tumors.

In a still further embodiment of the uses in accordance with the twenty-first and twenty-second aspect of the invention the cells, in particular the cells forming the tumor or parts thereof, are resistant, in particular multiple resistant against drugs, preferably anti-tumor agents and more preferably cytostatics.

In a preferred embodiment of the uses in accordance with the twenty-first and twenty-second aspect of the invention the cells are expressing, preferably are over-expressing the membrane-bound transport protein P-glycoprotein and/or MRP.

In a further embodiment of the uses in accordance with the twenty-first and twenty-second aspect of the invention the cells are either p53-positive or p53-negative.

In an embodiment of the uses in accordance with the twenty-first and twenty-second aspect of the invention the oncogene protein comprises, compared to the wildtype oncogene protein E1A, one or several mutations or deletions, whereby the deletions are preferably those selected from the group comprising deletions of the CR3 region and deletions of the N-terminus and deletions of the C-terminus. It is contemplated that the E1A oncogene protein is capable of binding to Rb.

In a further embodiment of the uses in accordance with the twenty-first and twenty-second aspect of the invention the oncogene protein comprises, compared to the wildtype oncogene protein, one or several mutations or deletions, whereby the deletion is preferably one in the CR1 region and/or CR2 region. It is contemplated that the oncogene protein E1A is incapable of binding to Rb.

In an embodiment of the uses in accordance with the twenty-first and twenty-second aspect of the invention the viral oncogene protein, in particular E1A, is under the control of a tissue-specific and/or tumor-specific promoter.

In a further embodiment of the uses in accordance with the twenty-first and twenty-second aspect of the invention the virus, in particular the adenovirus, is coding for YB-1.

In a still further embodiment of the uses in accordance with the twenty-first and twenty-second aspect of the invention YB-1 is under the control of a tissue-specific and/or tumor-specific promoter.

In a preferred embodiment of the uses in accordance with the twenty-first and twenty-second aspect of the invention the virus, in particular the adenovirus, codes for at

least one protein which is selected from the group comprising E4orf6, E4orf3, E1B55k and adenoviral E3ADP protein.

In an alternative embodiment of the uses in accordance with the twenty-first and twenty-second aspect of the invention the cells contain YB-1 in the nucleus, in particular the cells forming the tumor or part thereof comprise YB-1 in the nucleus.

In a further embodiment of the uses in accordance with the twenty-first and twenty-second aspect of the invention the tumor contains YB-1 in the nucleus after induction of the transport of YB-1 into the nucleus.

In a preferred embodiment of the uses in accordance with the twenty-first and twenty-second aspect of the invention the transport of YB-1 into the nucleus is caused by at least one measure, whereby the measure is selected from the group comprising irradiation, administration of cytostatics and hyperthermia.

In a particularly preferred embodiment of the uses in accordance with the twenty-first and twenty-second aspect of the invention the measure is applied to a cell, an organ or an organism.

In a preferred embodiment of the uses in accordance with the twenty-first and twenty-second aspect of the invention the virus, in particular the adenovirus, is selected from the group comprising AdΔ24, dl922-947, E1Ad/01/07, dl1119/1131, CB 016, dl520 and viruses which are lacking an expressed viral E1A oncogene which is capable of binding a functional Rb tumor suppressor gene product.

In a twenty-third aspect the problem is solved by the use of a virus, preferably the adenovirus, for the manufacture of a medicament, whereby the virus, in particular the adenovirus, is adapted such that the replication is controlled through or by YB-1 mediated activation of the E2-late promoter, preferably predominantly controlled by the activation of the E2-late promoter. In an embodiment YB-1 is either a transgenic YB-1 or a cellular YB-1, in particular a cellular deregulated YB-1 or deregulated YB-1. A transgenic YB-1 is preferably a YB-1 which is expressed in a cell by a vector, in particular by a or the adenovirus. The E2-late promoter is preferably the adenoviral E2-late promoter as contained in wildtype adenovirus, or an E2-late promoter as used in connection with the expression of the transgens as described herein.

In a twenty-fourth aspect the problem is solved by the use of a virus, in particular the adenovirus, for replication in cells which contain YB-1 in the nucleus, whereby the virus, in particular the adenovirus, is adapted such that the replication is controlled by YB-1 through the activation of the E2-late promoter, preferably predominantly by the

activation of the E2-late promoter. In an embodiment the YB-1 is either a transgenic YB-1 or a cellular YB-1, in particular a cellular deregulated or deregulated YB-1. A transgenic YB-1 is preferably a YB-1 which is expressed in a cell by a vector, in particular a or the adenovirus. The E2-late promoter is preferably the adenoviral E2-late promoter as present in wildtype adenovirus, or an E2-late promoter as used in connection with the expression of transgenes as described herein.

In a preferred embodiment of the twenty-third and/or twenty-fourth aspect of the present invention the adenovirus is adapted as disclosed herein, particularly adapted such that it may be used in accordance with the present invention.

In a twenty-fifth aspect the problem is solved by a viral oncogene protein, in particular an isolated viral oncogene protein, whereby the viral oncogene protein has the following characteristics:

a) transactivation of at least one viral gene in YB-1 nucleus positive cells which is selected from the group comprising E1B55k, E3ADP and E4orf6 and E4orf4; and

b) no induction of YB-1 in a cell nucleus, in particular in the cell nucleus of the cell in which the viral oncogene protein is present.

In an embodiment the viral oncogene protein is E1A.

In a further embodiment the viral oncogene protein comprises, compared to the wildtype oncogene protein, one or several mutations or deletions, whereby the deletions are preferably those selected from the group comprising deletion of the CR3 region, deletion of the N-terminus and deletion of the C-terminus.

In an embodiment the induction of YB-1 through the viral oncogene protein does not occur under the proviso that E4orf6 and/or E1B55kD is/are not present in the cell comprising said nucleus.

It is contemplated that the viral oncogene protein is capable of binding to Rb.

In an alternative embodiment the viral oncogene protein comprises one or several mutations or deletions, whereby the deletion is preferably one in the CR1 region and/or the CR2 region of the E1A oncogene protein. It is contemplated that the viral oncogene protein is incapable of binding to Rb.

In a twenty-sixth aspect the invention is related to the use of a viral replication system, in particular an adenoviral replication system comprising a nucleic acid coding for a virus, in particular an adenovirus, as used in accordance with the present invention, and comprising a nucleic acid of a helper virus, whereby the nucleic acid of the helper virus comprises a nucleic acid sequence coding for YB-1.

In an embodiment the viral nucleic acid, in particular the adenoviral nucleic acid, and/or the nucleic acid of the helper virus is present as replicable vector.

In a twenty-seventh aspect the invention is related to the use of a nucleic acid coding for a virus, in particular an adenovirus, as used in accordance with the present invention, for the manufacture of a medicament, in particular for the manufacture of a medicament for the treatment of tumors.

In a preferred embodiment the cells, in particular the cells forming the tumor or parts thereof, show a resistance, in particular a multiple resistance against drugs, in particular anti-tumor agents and more particularly cytostatics.

In a twenty-eighth aspect the present invention is related to the use of a nucleic acid coding for a virus, in particular an adenovirus, as used in accordance with the present invention, for the replication in cells which contain YB-1 in the nucleus, whereby the virus is replication deficient in cells which do not contain YB-1 in the nucleus or which do not comprise YB-1 in the nucleus independent of the cell cycle or which do not comprise any deregulated YB-1, and whereby the virus codes for an oncogene or an oncogene protein which at least transactivates one viral gene, preferably an adenoviral gene in YB-1 nucleus positive cells, whereby the gene is selected from the group comprising E1B55kDa, E4orf6, E4orf3 and E3ADP.

In a twenty-ninth aspect the problem is solved by the use of a nucleic acid coding for a virus, in particular an adenovirus, as used in accordance with the invention, for the manufacture of a medicament, whereby the virus is adapted such that the replication is controlled by YB-1 through the activation of the E2-late promoter, preferably predominantly through the activation of the E2-late promoter. In an embodiment the YB-1 is either a transgenic YB-1 or a cellular, in particular cellular deregulated, or deregulated YB-1. A transgenic YB-1 is preferably a YB-1 which is expressed in a cell by a vector, in particular by a or the adenovirus. The E2-late promoter is preferably the adenoviral E2-late promoter such as contained in wildtype adenovirus, or an E2-late promoter as used in connection with the expression of transgenes described herein.

In a thirtieth aspect the problem is solved by the use of a nucleic acid coding for a virus, in particular an adenovirus, as used in accordance with the present invention, for the replication in cells, whereby the virus is adapted so that the replication is controlled by YB-1 through the activation of E2-late promoter, preferably predominantly through the activation of the E2-late promoter. In an embodiment YB-1 is either a transgenic YB-1 or a cellular, in particular cellular deregulated YB-1. A transgenic YB-1 is preferably one which is expressed in a cell by a vector, preferably by a or the adenovirus. The E2-late promoter is preferably the adenoviral E2-late promoter as present in wildtype adenovirus, or an E2-late promoter as used in connection with the expression of transgenes as described herein.

In a thirty-first aspect the problem is solved by the use of a vector comprising one of the previously described nucleic acids, for the use in accordance with the twenty-first or twenty-second aspect of the present invention.

In a thirty-second aspect the invention is related to the use of an agent interacting with YB-1 for the characterisation of cells, of cells of a tumor tissue or of patients in order to determine whether they shall be contacted and/or treated with a virus, in particular an adenovirus, as used in accordance with the present invention.

In an embodiment the agent is selected from the group comprising antibodies, anticalines, aptamers, aptazymes and spiegelmers.

In a thirty-second aspect the problem is solved by the use of the viral oncogene protein in accordance with the present invention, or a nucleic acid coding therefor, for the manufacture of a virus, in particular of an adenovirus, as used in connection with the uses in accordance with the twenty-first and twenty-second aspect of the present invention.

In an embodiment the virus comprises a nucleic acid coding for a transgene.

In a further embodiment the virus comprises the translation product and/or the transcription product of a transgene.

In a preferred embodiment the nucleic acid of the adenoviral replication system and/or the nucleic acid of the helper virus comprises a transgene or a nucleic acid coding for a transgene.

In a still further embodiment the nucleic acid comprises a transgen or a nucleic acid coding for a transgene.

In an alternative embodiment the transgene is selected from the group comprising prodrugs, cytokines, apoptosis-inducing genes, tumor suppressor genes,

genes for metalloproteinase inhibitors and genes for angiogenesis inhibitors and for tyrosine kinase inhibitors.

In an embodiment the transgene is selected from the group comprising nucleic acids for siRNA, for aptamers, for antisense molecules and for ribozymes, whereby the siRNA, the aptamers, the antisense molecules and/or the ribozymes are directed against the target molecule.

In a further embodiment the target molecule is selected from the group comprising resistance relevant factors, anti-apoptosis factors, oncogenes, angiogenesis factors, DNA synthesis enzymes, DNA repair enzymes, growth factors and their receptors, transcription factors, metalloproteinases, in particular matrix metalloproteinases, and plasminogen activator of the urokinase type. In an embodiment the resistance relevant factors are preferably selected from the group comprising P-glycoprotein, MRP and GST, and also comprise the nucleic acids coding therefor. In an embodiment the anti-apoptosis factors are selected from the group comprising BCL2, and also comprise the nucleic acids coding therefor. In an embodiment the oncogenes are selected from the group comprising Ras, in particular mutated Ras, Rb and MYC, and also comprise the nucleic acids coding therefor. In an embodiment the angiogenesis factors are selected from the group comprising VEGF and HMG proteins, and also comprise the nucleic acids coding therefor. In an embodiment the DNA synthesis enzymes are selected from the group comprising telomerase, and also comprise the nucleic acids coding therefor. In an embodiment the DNA repair enzymes are selected from the group comprising Ku-80, and also comprise the nucleic acids coding therefor. In an embodiment the growth factors are selected from the group comprising PDGF, EGF and M-CSF, and also comprise the nucleic acids coding therefor. In a further embodiment the receptors are preferably those for growth factors, whereby preferably the growth factors are selected from the group comprising PDGF, EGF and M-CSF, and also comprise the nucleic acids coding therefor. In an embodiment the transcription factors are selected from the group comprising YB-1, and also comprise the nucleic acids coding therefor. In an embodiment the metalloproteinases are in particular matrix metalloproteinases. In a preferred embodiment the matrix metalloproteinases are selected from the group comprising MMP-1 and MMP-2, and also comprise the nucleic acids coding therefor. In an embodiment the plasminogen activators of the urokinase type are selected from the group comprising uPa-R, and also comprise the nucleic acids coding therefor.

In a still further embodiment the medicament further comprises at least one pharmaceutically active compound.

In a preferred embodiment of any aspect of the present invention the pharmaceutically active compound is selected from the group comprising cytokines, metalloproteinase inhibitors, angiogenesis inhibitors, cytostatics and cell cycle inhibitors and tyrosine kinase inhibitors.